

# Advances in treating acute asthma exacerbations in children

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## Purpose of review

Asthma continues to be a major chronic disease in children, and acute asthma exacerbations are common. Although the basic therapy of asthma exacerbations has not changed, recent studies have demonstrated improved outcomes with different modes of delivery of medications, improved patients' self-management of their asthma, and recognition of risk factors for severe exacerbations.

## Recent findings

Recent studies in children have shown that written action plans based on symptom recognition are more effective than action plans based on peak expiratory flows. Bronchodilator administration by metered-dose inhaler is becoming the preferred therapy for treating mild-to-moderate asthma exacerbations in the emergency department, but nebulizers may still have a role in home and inpatient asthma management. High-dose inhaled corticosteroids may be as effective as oral corticosteroids for acute asthma exacerbations. A novel treatment strategy has titrated combination therapy with budesonide and formoterol for both maintenance and relief of symptoms. Lastly, the contributions of obesity and genetic variation to severe asthma exacerbations are becoming known, and noninvasive positive pressure ventilation has become an option for patients in severe asthma exacerbations.

## Summary

Improvements in management strategies can significantly improve outcomes in children with asthma.

## Keywords

action plans, corticosteroids, metered-dose inhalers, noninvasive ventilation

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## Introduction

After increasing for decades, the prevalence of asthma appears to have stabilized, and rates of asthma hospitalizations and deaths have started to decrease. Nevertheless, asthma remains the leading chronic illness of children in the United States. In 2006, over 6.8 million children under age 18 years had asthma, and 4.1 million had an asthma attack that year [1]. The annual cost of asthma in the United States is estimated to be \$19.7 billion, with \$3.2 billion devoted to caring for children less than 18 years of age [2]. A large fraction of this cost is attributed to emergency department (ED) visits and hospitalizations. Thus, considerable effort has been committed to exacerbation prevention and home management.

Treatment of asthma exacerbations includes early recognition and initiation of therapy with bronchodilators and anti-inflammatory corticosteroids. Recent reviews and expert panels have addressed the general evaluation and specific medical treatment of acute asthma exacerbations in children [3–5]. This article will focus on recent advances and innovations related to caring for children

with acute asthma exacerbations at home, in the ED, and during hospitalizations.

## Written action plans

National and international asthma guidelines universally endorse written self-management plans for every asthma patient. Details of these plans vary, however, with the United States [6], Canadian [7], and British guidelines [8] favoring peak flow-based action plans, but Australian guidelines [9] preferring symptom-based plans. Written action plans are typically one facet of asthma education, which also includes medical review, identification and avoidance of triggers, explanation of medications and delivery systems, early recognition of signs of deterioration, and instructions for the prevention and management of exacerbations. Although asthma education clearly is beneficial for adults [10] and children [11,12], it is less clear how the provision of a written action plan contributes to this effect. A recent meta-analysis by Bhogal *et al.* [13] addressed this question [14••].

Literature search by these authors identified four studies [15–18] aggregating 355 children that compared

symptom-based action plans with peak flow-based action plans, with all other educational cointerventions kept equal. The meta-analysis demonstrated that symptom-based action plans were superior to peak flow-based action plans in children and adolescents in the context of asthma education and regular medical review. Children using symptom-based written action plans had lower risk of exacerbations requiring acute care visits [relative risk (RR), 0.73; 95% confidence interval (CI), 0.55–0.99]. Subgroup analyses failed to identify significant group differences in written action plan format (number of steps or color) or intensity of peak-flow monitoring on the risk of a patient requiring an acute care visit. In the study [18] that addressed patient preference, symptom monitoring was favored over peak-flow monitoring by children, but parents showed no preference. Only one study [19] compared a written action plan (peak flow-based) with no plan in 68 children with moderate persistent asthma. Children with action plans had reductions in the mean difference of school days missed, nocturnal awakenings, and symptom scores. Thus, although symptom-based action plans appear to be superior to peak flow-based action plans in children and adolescents in the context of asthma education and regular medical review, there is insufficient information to conclude that provision of a written action plan as compared with none reduces acute care visits and symptoms [13,14\*\*].

### **Bronchodilator delivery**

Inhaled bronchodilators are a cornerstone of treatment of acute exacerbations, and it is clear that inhaled administration allows for selective treatment to the lungs while minimizing systemic effects of the medication [20]. Bronchodilator therapy can be delivered either by nebulized aerosol or by pressurized metered-dose inhaler (MDI). In children, there is no proven benefit of nebulized aerosol treatment over MDI [6,20–22], provided that adequate MDI doses are given. Dose-ranging techniques have shown that it takes between 4 and 10 puffs of an MDI bronchodilator to provide acute efficacy similar to a single nebulizer treatment [23–25]. Several well conducted controlled studies [20,26,27] have been performed in children with acute asthma in the ED setting. In two prospective double-blinded trials, children over 5 years of age who presented with mild acute asthma were randomized to receive bronchodilator therapy either via an MDI with a large volume spacer or via a nebulizer [26,27]. Similar improvements in pulmonary function, clinical asthma score, and respiratory rate were found, suggesting that these treatment modalities were equally effective in this population. A meta-analysis assessed six similar trials performed in 491 children under 5 years of age with acute exacerbations of wheezing or asthma in the ED [28]. Patients who received  $\beta$ -agonists by MDI and valved holding chamber showed a significant

decrease in the admission rate compared with those receiving nebulizer treatments [odds ratio (OR), 0.42; 95% CI, 0.24–0.72]; this decrease was even greater among children with moderate-to-severe exacerbations (OR, 0.27; 95% CI, 0.13–0.54).

No study has yet compared nebulized versus MDI bronchodilator in the outpatient setting. In the ED, patients are instructed and monitored on correct use of the devices. In the absence of such coaching, one study [29] found that 44% of children and families self-administering albuterol by MDI and holding chamber performed multiple steps incorrectly. Only 24% demonstrated completely perfect administration. Similarly, when their MDI technique was evaluated, 76% of adult patients using an MDI for at least a month made at least one error when demonstrating its use, and 28% made critical errors that would result in almost no medication reaching the lungs [30]. In addition, studies [31] show that most patients prescribed MDIs do not know how to determine when the MDI is empty. This shortcoming creates the risk that a patient may use an empty MDI during an acute exacerbation. Even with adequate supervision, correct MDI technique, and a full MDI device, hospitalized children may benefit from nebulized  $\beta$ -agonists over MDI forms. The potential for suboptimal MDI technique may increase with increasing severity of exacerbations. Moreover, the nebulized route allows continuous bronchodilator administration, which has been shown to decrease therapist time [20] and to hasten patient recovery time and to reduce length of stay [32]. Thus, although MDI  $\beta$ -agonists may be efficacious in the ED setting, there remain valid reasons to continue using nebulized bronchodilators during home flares and more severe asthma exacerbations in the hospital.

### **Inhaled corticosteroid doses**

In addition to starting inhaled  $\beta_2$ -agonists as needed, early guidelines advised doubling the doses of inhaled corticosteroid (ICS) during asthma exacerbations in patients already receiving ICS therapy. This practice has not been found to be effective in reducing the severity or preventing progression of exacerbations in adults or in children [33–37]. In contrast, preliminary evidence suggests that quadrupling the dose of an ICS for 7 days, starting at the first appearance of worsening symptoms, may obviate the need for oral corticosteroids. A double-blind, multicenter, parallel-group study randomized adults to one of the following treatments for a period of 6 months: budesonide 400  $\mu$ g twice daily and placebo four times per day at the start of an exacerbation (group 1;  $n=67$ ); budesonide 100  $\mu$ g twice daily and budesonide 200  $\mu$ g four times per day during exacerbations (group 2;  $n=67$ ); and budesonide 100  $\mu$ g twice daily and placebo four times per day during exacerbations (group 3;  $n=75$ ). Low-dose daily budesonide with

four-fold increase during exacerbations (group 2) was as effective as high daily dosing (group 1) in reducing duration of exacerbations and oral corticosteroid use [38]. In a separate study [35], 150 children (aged 1–14 years) received budesonide 200–400 µg four times daily in combination with a  $\beta$ -agonist at the first sign of an asthma exacerbation, and the budesonide dosage was decreased over 4–8 days. Children were followed on this regimen for a median of 1 year (range 3 months–5 years). The total number of asthma exacerbations during the entire follow-up period was 1061; of these, 1001 (94%) were successfully controlled with the protocol. Only 11 children required oral corticosteroids during treatment with the acute budesonide protocol as compared with 101 children who used oral corticosteroids in 3 months preceding initiation of the protocol. These studies suggest a role for more substantial increases in ICS doses during acute exacerbations.

Emerging data also suggest that high doses of ICS may be as effective as systemic corticosteroids in the treatment of acute asthma exacerbations in children [39<sup>••</sup>]. Four randomized, double-blind studies involving 206 children have evaluated the use of inhaled budesonide in children presenting to an ED with mild-to-moderate asthma flares. The addition of a single dose of nebulized budesonide (2000 µg) to therapy with prednisone (1 mg/kg to maximum 50 mg) and nebulized albuterol resulted in more rapid discharge from the ED or hospital compared with conventional albuterol and prednisone therapy [40]. When used without systemic corticosteroids, inhaled budesonide (400 µg by MDI and spacer every 30 min for three doses) added to nebulized albuterol significantly improved respiratory status at 2 h, reduced the need for aminophylline infusion and systemic corticosteroid therapy, and prevented hospitalizations [41]. Similarly, replacement of a single oral dose of prednisolone (2 mg/kg) with three doses of nebulized budesonide (800 µg at 30-min intervals) resulted in more rapid rate of recovery, shortened ED stays, and reduced hospitalization rates in 2–12-year-old children experiencing moderate asthma exacerbations [42]. Acceleration of recovery with the use of inhaled budesonide continued after discharge from the ED following treatment of moderate asthma exacerbations [43]. The salutary acute effects of ICS have been more consistently documented with budesonide than with beclomethasone dipropionate or fluticasone [44], possibly due to differences in dissolution and lipophilicity of the agents [39<sup>••</sup>].

#### Oral corticosteroid doses

Current guidelines no longer suggest doubling the ICS dose during exacerbations, but recommend instead the initiation of short courses of oral steroids [6]. Nevertheless, there is a lack of consensus regarding the dosage and duration of corticosteroid therapy during acute asthma

exacerbations in children. The 2007 National Asthma Education and Prevention Program (NAEPP) guidelines recommend a duration of systemic corticosteroid treatment between 3 and 10 days [6]. This recommended range is fairly broad, and some recent clinical trials in children with mild-to-moderate exacerbations suggest that shorter durations of corticosteroid therapy may be as effective as longer durations [45–47]. One randomized prospective trial compared a 3-day with a 5-day course of oral prednisolone in 201 children discharged from the ED with asthma exacerbations [45]. During a 2-week follow-up, there were no significant differences in clinical asthma score, cough score, or asthma-related quality of life between these two groups. Two other studies compared single-dose dexamethasone therapy (0.6 mg/kg) with a 5-day course of oral prednisone (2 mg/kg/day) using randomized and blinded controlled study designs [46,47]. One of these trials used intramuscular dexamethasone [46], the other an oral formulation [47]. Both of these trials were conducted in children presenting to the ED with mild-to-moderate asthma exacerbations. There were no differences in clinical outcomes during the ED visit or on follow-up, suggesting that single-dose dexamethasone may be as effective as a longer course of prednisone [46,47]. These trials were adequately powered to show noninferiority; however, the populations in each trial were relatively small, involving 181 and 110 children, respectively.

During more severe exacerbations, there is little published evidence regarding corticosteroid dosage and duration. NAEPP guidelines do not offer a recommended steroid dosage for patients in impending respiratory failure. Some authors, however, recommend dosages as high as 4–6 mg/kg/day of systemic prednisone or prednisolone [3,48], significantly above the 2 mg/kg/day suggested by the NAEPP guidelines for less severe exacerbations [6]. Oral corticosteroid formulations have been shown to be as beneficial as intravenous formulations in less severely ill children [6]. However, in critically ill children who are receiving high-dose  $\beta$ -agonist therapy, vomiting is common and gastrointestinal absorption is frequently impaired. In these situations, intravenous corticosteroids are preferred [6].

#### Symbicort maintenance and relief therapy protocols

The desire to deliver increased anti-inflammatory therapy during acute asthma exacerbations has led to the consideration of using the combination of budesonide/formoterol as both maintenance and symptomatic therapy. Formoterol is a long-acting  $\beta_2$ -agonist with an onset of action comparable to that of short-acting  $\beta_2$ -agonists. One inhaler therapy adjusts both ICS and  $\beta_2$ -agonist therapy automatically in response to patients' changing needs and so may be more effective than independent modification of separate maintenance and

reliever inhalers. Five large-scale, double-blind clinical trials and one open-label, dose-titration study including over 15 000 asthma patients aged at least 12 years have demonstrated the superior efficacy and safety of single-inhaler budesonide/formoterol maintenance and reliever therapy compared with two-fold to four-fold higher doses of ICS (budesonide) and short-acting  $\beta_2$ -agonist [49–51] and with similar or higher doses of maintenance budesonide/formoterol [49,52,53] or salmeterol/uticasone [50,54,55] and short-acting  $\beta_2$ -agonists as needed. These studies used the Symbicort Turbuhaler device (AstraZeneca, Lund, Sweden), providing 160/4.5 or 80/4.5  $\mu\text{g}$  per inhalation, and have coined the term SMART for Symbicort Maintenance and Relief Therapy. With SMART, in addition to a maintenance dose of one inhalation twice daily [49] or two inhalations once daily [50,51], additional inhalations for symptom relief are taken in the same way as patients previously used their short-acting  $\beta_2$ -agonists. Protocols utilizing maintenance and as-needed use of budesonide/formoterol in one inhaler reduced the risk of experiencing severe exacerbations by 39–54% compared with increasing the dose of budesonide [49–51], by 45% compared with fixed-dose budesonide/formoterol and a short-acting  $\beta_2$ -agonist [49], and by 25% compared with increasing the dose of fluticasone/salmeterol [54]. The use of budesonide/formoterol as maintenance and reliever therapy decreased oral corticosteroid use by 41% compared with a higher fixed dose of budesonide/formoterol and short-acting  $\beta$ -agonist [52] and by 23–45% compared with a fixed dose of fluticasone/salmeterol and short-acting  $\beta$ -agonist [52,55]. The rate of severe asthma exacerbations requiring ED care or hospitalization was also reduced with budesonide/formoterol maintenance and reliever therapy compared with comparator therapies [50,52,53,55].

Bisgaard *et al.* [56] analyzed SMART in the subgroup of pediatric patients enrolled in a large 12-month, randomized, double-blind, and parallel-group trial conducted at 41 centers in 12 countries [49]. Children aged 4–11 years with asthma for 6 months or longer and at least one clinically important asthma exacerbation in the 12 months before study entry were enrolled. All patients had used ICS at a constant dose for at least 3 months (200–500  $\mu\text{g}/\text{day}$ ). Following a run-in period during which patients used their previous ICS and terbutaline as needed, patients were randomized to one of the three treatments: budesonide/formoterol (Symbicort Turbuhaler) 80/4.5  $\mu\text{g}$  once daily and additional doses as needed (SMART;  $n = 118$ ); budesonide/formoterol 80/4.5  $\mu\text{g}$  once daily and terbutaline 0.4 mg for rescue medication (fixed combination;  $n = 117$ ); or a four-fold higher maintenance dose of budesonide 320  $\mu\text{g}$  once daily and terbutaline 0.4 mg for rescue medication (fixed-dose budesonide;  $n = 106$ ). Patients were not allowed to use more than eight inhalations of the study medication during one

single day (i.e., not more than seven as-needed inhalations per day in addition to their daily maintenance treatment). SMART prolonged the time to first exacerbation versus the fixed-dose budesonide and fixed-dose combination regimens. Rates of exacerbation requiring medical intervention were reduced by 70–79% with SMART versus the fixed-dose budesonide and fixed-dose combination therapy. Total days of oral steroids were reduced by 77 and 86% with SMART compared with the two fixed-dose regimens. Mild exacerbation days and nighttime awakenings were also lower with SMART. Adverse events were not increased in the SMART group, and yearly growth improved by 1.0 cm with SMART compared with fixed-dose budesonide [56].

The 2007 updated guidelines from the Global Initiative for Asthma (GINA) recommend the use of budesonide/formoterol as both maintenance and reliever therapy in patients with persistent asthma, with evidence level category A ([57]; p. 62). It should be noted that SMART is only approved for use with the Turbuhaler device [58<sup>••</sup>], which is not available in the United States. Although budesonide/formoterol 80/4.5 and 160/4.5  $\mu\text{g}$  in a pressurized MDI is approved in the United States for fixed-dose maintenance therapy of asthma in patients at least 12 years of age, the suitability of this delivery device for SMART has not been investigated.

### Severe asthma exacerbations

Severe asthma exacerbations are one of the most common admission diagnoses to a pediatric ICU. Recently, clinical phenotypes have been identified that may be important in influencing a child's hospital course [59–61]. In particular, obesity may be an important confounder in children with asthma [59,60]. Genetic variations in the population may also be important in influencing response to therapy for acute asthma [62]. Recently, we identified a population of children admitted to the ICU with severe asthma who were slow-responders to  $\beta$ -agonist therapy [61]. We investigated the genotypes in this group of children and found that there were genetic polymorphisms of the  $\beta_2$ -adrenergic receptor that were associated with improved response to  $\beta$ -agonist therapy during severe exacerbations [62]. Specifically, children homozygous for glycine instead of arginine at amino acid position 16 of the  $\beta_2$ -adrenergic receptor had significantly shorter ICU length of stay and duration of continuously nebulized bronchodilator therapy [62]. However, the sample size of this retrospective study was small ( $n = 37$ ) and included only 25% of eligible children. Larger studies are needed to investigate genetic influences in this population.

### Noninvasive positive pressure ventilation

Noninvasive positive pressure ventilation (NPPV) is a relatively new therapy for the treatment of respiratory

insufficiency in children [63,64,65<sup>•</sup>,66]. In asthma, NPPV is used to support the respiration of children with status asthmaticus as an alternative to endotracheal intubation in critically ill children [63,64,65<sup>•</sup>]. NPPV can be delivered either as continuous positive airway pressure or as bilevel positive airway pressure (BiPAP) that varies between higher inspiratory and lower end-expiratory pressures. During acute bronchospastic episodes, airways resistance and expiratory time constants are increased, and positive pressure helps to avoid airway collapse during exhalation [67,68]. Additionally, the positive pressure unloads fatigued respiratory muscles by reducing the pressure needed to initiate each breath [67,68]. During BiPAP ventilation, tidal breathing is also augmented. As NPPV uses a noninvasive interface, spontaneous breathing and upper airway function are preserved, thereby allowing a patient to spontaneously provide their own airway clearance [67,68]. This interface can be via either a nasal mask or a nasal oral mask. However, finding appropriately sized and well fitting masks can be challenging in the pediatric population [66]. The success of NPPV therapy requires some level of cooperation from the child to reduce air leakage around the mask interface and to maintain the positive pressure provided. Clinicians experienced with NPPV can typically achieve this cooperation using nonpharmacologic or distraction techniques, even in critically ill children [63,64,65<sup>•</sup>]. In some children, however, sedation may be required in order to facilitate tolerance of this therapy. Clinicians must then carefully consider the risks of sedation against the benefits of NPPV in a particular child.

There are several trials in adults examining the efficacy of NPPV for the treatment of acute asthma [68–70]. In these adult trials, NPPV was found to improve pulmonary function [69,70], improve gas exchange [68], and decrease hospitalization [70]. However, there are only a few published studies [63,64,65<sup>•</sup>] that report the use of NPPV in children with acute asthma. Two of these studies (one case series and one prospective cross-over study) [63,64] were conducted in children admitted to the ICU with acute asthma, and one case series [65<sup>•</sup>] was reported in a population of children presenting to the ED with severe asthma. The sample sizes in these studies were small, involving only a total of 98 children. However, each found an improvement in gas exchange and respiratory effort as quantified by respiratory rate, clinical asthma score, or both [63,64,65<sup>•</sup>]. Children received NPPV therapy in these trials for a relatively long duration. In the case series of children admitted to the ICU, the median duration of therapy was 26 h (range 6–70 h); and in the case series of children presenting to the ED, the average duration was 6 h. Fewer than 5% of the children required sedation for this therapy, and there were no adverse events noted [63,64,65<sup>•</sup>].

## Conclusion

In this review, we have highlighted some recent advances in the management of acute asthma in children. Acute exacerbations of asthma are a significant cause of morbidity in children. Despite the high prevalence of asthma, there are relatively few controlled studies examining the acute treatments for this disease. Even in the absence of novel therapies, however, improvements in management strategies, education, and patient adherence have the potential to significantly improve outcomes in this population.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 408–409).

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